CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202714Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	202714
Applicant Name	Onyx Therapeutics, Inc.
Date of Submission	9/27/2011
PDUFA Goal Date	7/27/2012
Proprietary Name /Established (USAN) Name	KYRPOLIS/carfilzomib
Dosage Forms / Strength	Vial containing 60 mg of a sterile lyophilized powder for solution injection
Applicant's Proposed Indication(s)	the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted OND Action Package, including:	
Division Director	Ann Farrell, MD
Medical Officer Review	Thomas Herndon, MD/Albert Deisseroth, MD/PhD
Statistical Review	Kallappa Koti, PhD/Mark Rothmann, PhD
Pharmacology Toxicology Review	Todd Palmby, PhD/J Hayes, PhD/ J Bray, PhD/Haleh Saber, PhD
CMC Review/OBP Review	W. Michael Adams, PhD/Josephine Jee, PhD/Janice Brown, MS/Youngsook Jeon, PhD/ Yi Tsong, PhD/ Sarah Pope-Miksinski, PhD
Microbiology Review	John Metcalfe, PhD/ Stephen E. Langille, PhD
Clinical Pharmacology Review	Bahru Habtemariam, PhD/Julie Bullock, PharmD/Christine Garnett, PhD
DDMAC	James Dvorsky
DSI	Anthony Orencia, MD/Tejashari Purohit Sheth, MD
CDTL Reviews	Albert Deisseroth, MD, PhD
OSE/DMEPA	Sara K Yee, PharmD/Yelena Maslov, PharmD/Kimberly De Fronzo/Irene Z Chan, PharmD
Other – Pediatrics Maternal Health Team Other- DCRDP	Elizabeth L. Durmowicz, MD/Hari C. Sachs, MD/Lisa Mathis, MD Preston M. Dunnmon, MD/Thomas Marcinzak, MD/Norman Stockbridge, MD

1. Introduction

This NDA was submitted on September 27, 2011 for carfilzomib for the treatment of patients with relapsed multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent. Carfilzomib is an irreversible proteasome inhibitor administered by intravenous injection. The only approved proteasome inhibitor (approved since 2003) for the treatment of multiple myeloma is Velcade (bortezomib).

The main trial results to support this indication are from a single arm trial enrolling 266 patients with multiple myeloma. This trial was supported by multiple other smaller single arm trials investigating dose/dosing regimen. This application is being considered for accelerated approval. The applicant has at least one ongoing large multicenter, randomized controlled trial to demonstrate clinical benefit. This trial is a randomized active controlled trial enrolling patients with multiple myeloma comparing carfilzomib, lenalidomide, dexamethasone with lenalidomide and dexamethasone. The primary endpoint is progression-free survival. This study is being conducted under a Special Procotol Assessment (SPA).

2. Background

There are multiple FDA-approved products for use in the treatment of multiple myeloma as shown in the table below.

Table 1. FDA Approved Drugs for Multiple Myeloma

Class	Drug	FDA Approval
Alkylating agents	Melphalan Cyclophosphamide	Regular Regular
Anthracyclines	Liposomal doxorubicin (Doxil™)	Regular
Nitrosureas	Carmustine	Regular
ImiDs	Thalidomide Lenalidomide	Accelerated approval: Restricted Distribution (Subpart H)
Proteasome Inhibitors	Bortezomib	Accelerated approval then converted to Regular

Steroids such as prednisone and dexamethasone are frequently used in alone or in combination with the agents in the table above. There is extensive information on the use of these agents in the literature.

3. CMC/Device

The CMC review staff has concluded that:

The Applicant has resolved all outstanding CMC issues, and this application is recommended for approval with respect to the chemistry, manufacturing, and controls (CMC).

The recommended storage conditions are presented in the labeling statements: "Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F). Retain in original package to protect from light."

The stability data appears to provide adequate support for the proposed shelf-life of 18 months or expiration date and the labeling statements for the drug product storage conditions.

4. Nonclinical Pharmacology/Toxicology

Nonclinical review staff has determined that there are no outstanding issues that would preclude approval.

Toxicity signals observed include cardiac toxicity, azotemia, acute phase response, gastrointesintal toxicity, and hematological effects.

Nonclinical reviews state: *Carfilzomib was not genotoxic in the reverse mutation bacterial test (Ames) and the mouse micronucleus test. Carfilzomib causes an increase in chromosome structural aberrations in human peripheral blood cells at ≥0.04 µg/mL and at ≥2.4 µg/mL in vitro in the absence and presence of metabolic activation, respectively.*

Regarding teratogenicity: *Carfilzomib caused no overt teratogenicity in pregnant rats.*

5. Clinical Pharmacology/Biopharmaceutics

From the summary section of the Clinical Pharmacology Review:
In vitro studies showed carfilzomib is metabolized in plasma by protein peptidase and epoxide hydrolysis. In total, these studies show the exposure to carfilzomib will not be influenced by other drugs and carfilzomib will not influence exposure to other drugs.

The ADME characteristics of carfilzomib were not conducted in humans; ADME data were available from a rat study. The rat ADME study showed 30.5% of the administered drug undergoes biliary elimination while about 26% of the administered drug is eliminated by the kidneys. A renal impairment study in cancer patients showed the Cmax and AUC of carfilzomib were similar across all renal function categories including patients with normal renal function and those with mild, moderate, and severe renal impairment, and those patients on chronic dialysis.

The proportion of the administered drug that undergoes biliary elimination has not been evaluated in humans. In addition, the occurrence of grade 3/4 ALT elevations in 6.4% of patients in the pivotal phase 2 study suggests those patients with pre-existing hepatic impairment maybe at an increased risk of liver toxicity when treated with carfilzomib. In order to characterize the influence of hepatic function on the safety and pharmacokinetics of carfilzomib, a post marketing study in patients with hepatic impairment will be requested.

From the review regarding proteasome inhibition:
Dose-dependent inhibition was observed in RBCs and PBMCs after the first dose and appeared to plateau at approximately 75% proteasome inhibition at doses of 11 mg/m2 and above. Following repeat carfilzomib doses, proteasome inhibition was increased to about 90% in both RBCs and PBMCs.

From the review regarding half-life:
Carfilzomib has a very short half life (0.45 to 1 hour), and no drug accumulation is expected following multiple dose drug administration.

From the review regarding protein-binding (PPB):
The mean PPB was 98.0%, 97.6%, 98.3%, 98.2% and 97.9% in patients with normal renal function, mild, moderate, and severe renal impairment, and dialysis subjects, respectively.

From the IRT review:
No large change in QTc (i.e., >20 ms) was detected in this trial following administration of carfilzomib (15 mg/m2, 20 mg/m2 and 36 mg/m2).

There are several clinical pharmacology postmarketing commitments. Please see action letter for these commitments.

6. Clinical Microbiology

The product quality microbiology review discipline recommends approval.

7. Clinical/Statistical-Efficacy

The main trial to support this application is a single-arm, multicenter clinical trial enrolling 266 patients with relapsed multiple myeloma who had received at least two prior therapies, including bortezomib and an immunomodulatory agent (thalidomide or lenalidomide). Carfilzomib was administered intravenously over 2 to 10 minutes on 2 consecutive days

weekly for 3 weeks, followed by a 12-day rest period (28 day treatment cycle). Treatment was continued until disease progression, unacceptable toxicity, or completion of a maximum of 12 cycles. Patients received 20 mg/m2 at each dose in cycle 1, and 27 mg/m2 in subsequent cycles.

To reduce the incidence and severity of infusion reactions associated with carfilzomib administration, dexamethasone (4 mg orally or intravenously) was administered prior to all carfilzomib doses during the first cycle and prior to all carfilzomib doses during the first dose-escalation (27 mg/m2) cycle. Dexamethasone premedication was re-instated if these symptoms reappeared during subsequent cycles.

The primary efficacy endpoint was overall response rate (ORR), determined by Independent Review Committee assessment using International Myeloma Working Group criteria. The ORR was 22.9% (95% CI: 18.0, 28.5), consisting of 1 complete response, 13 very good partial responses and 47 partial responses. The median response duration was 7.8 months (95% CI: 5.6, 9.2).

8. Safety

Safety data was evaluated in 526 patients with relapsed multiple myeloma who received carfilzomib as monotherapy. Patients received a median of 4 treatment cycles with a median cumulative carfilzomib dose of 993.4 mg. The most common adverse reactions (incidence of 30% or greater) observed in clinical trials of patients with multiple myeloma were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. Serious adverse reactions were reported in 45% of patients. The most common serious adverse reactions were pneumonia, acute renal failure, pyrexia, and congestive heart failure. There were 37/526 (7%) deaths on study. The most common causes of death, other than underlying disease, were cardiac (5 patients), end-organ failure (4 patients), and infection (4 patients).

In single arm trials it is difficult to state with certainty whether the adverse reactions observed are attributable to the drug, underlying (non-myeloma disease), or prior therapy.

However, the review team identified several areas for review: cardiovascular events, hepatotoxicity, and pulmonary toxicity.

Cardiac Adverse Events
Deaths during the first 30 days: The most common non-myeloma cause was cardiac events including sudden death, myocardial infraction, arrest, and congestive heart failure. Most common cause of treatment discontinuation excluding disease progression: cardiac.

Hepatotoxicity
Two patients who enrolled in the trials with normal liver enzymes died after they were treated with carfilzomib and developed liver enzyme elevations/failure. Other patients experience liver enzyme elevation although they did recover. No Hy's Law cases were identified.

Pulmonary
The second common cause of treatment discontinuation excluding disease progression: pulmonary (dyspnea and pneumonia). Two patients developed pulmonary arterial hypertension.

Infusion Reactions with Carfilzomib:
During the course of carfilzomib drug development, the Applicant identified symptoms and adverse events which occur within 24-48 hours of administration of carfilzomib. These adverse events include: fever, chills, rigors, pyrexia, myalgias, arthralgias, dyspnea, hypotension, hypoxia and flushing. In an attempt to reduce this toxicity, the Applicant modified the clinical protocols by adding premedication with dexamethasone along with the administration of oral and intravenous hydration. The amount of dexamethasone per cycle was 24 mg (4 mg per treatment) and much lower than low dose dexamethasone given in other multiple myeloma treatment regimens. This 4 mg pre-carfilzomib dexamethasone dose was not completely successful at preventing infusion reactions.

9. Advisory Committee Meeting

This product was discussed at an Oncologic Drugs Advisory Committee meeting on June 20, 2012. The Committee voted 11 (yes) to 1 (abstain) that the available clinical data demonstrate a favorable risk-benefit profile for carfilzomib.

10. Pediatrics

Because carfilzomib has orphan drug designation for the indication being sought, the sponsor is exempt from the requirements under the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

Recommended regulatory action: Accelerated Approval.

The applicant has agreed to submit the complete study report and datasets for the ongoing ASPIRE trial (PX-171-009) as a post marketing requirement to demonstrate clinical benefit. This trial is a randomized active controlled trial enrolling patients with multiple myeloma comparing carfilzomib, lenalidomide, dexamethasone with lenalidomide and dexamethasone. The primary endpoint is progression-free survival.This study protocol is being conducted under an SPA and the study has completed accrual. The Applicant estimates the submission date as June 2014.

Risk Benefit Assessment
The risk benefit assessment suggests that carfilzomib is effective for the treatment of patients with multiple myeloma whose disease has relapsed after receiving established and approved treatments such as bortezomib, lenalidomide, thalidomide, mephalan and other alkylating agents. The most common side effects include: fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. The following adverse reactions were identified as being particularly concerning: cardiac, pulmonary, hepatic, thrombocytopenia, and infusion reactions. The latter list is included in the warnings and precautions section of the labeling. Additionally the cardiac and pulmonary will be the subject of ongoing PMRs under FDAAA. The risk-benefit profile was also assessed by the clinical review team and Dr. Farrell, and I concur with their recommendations to approve this application.

Recommendation for Post marketing Risk Management Activities
Routine post-marketing surveillance except for enhanced pharmacovigilance for cardiac adverse reactions, pulmonary adverse reactions, hepatoxicity

Cardiac and pulmonary testing will be incorporated into a planned phase 3 trial in order to better understand the potential cardiac and pulmonary risks of carfilzomib.

Recommendation for other Post marketing Study Requirements/ Commitments
See action letter.

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/s/

TAMY E KIM
07/20/2012

RICHARD PAZDUR
07/20/2012